*Essay*

# A Critical Evaluation of Factors Related to the Recent Outbreak of Bordetella Pertussis in Children in the USA

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## Abstract

The recent outbreak of Bordetella Pertussis in the US confirms that the infection is still very much endemic in the country. Outbreaks were recorded despite rates of immunization at more than 80% among the population. While it could be argued that declining immunity is a contributory factor to the increase in the incidence of pertussis, evidence suggests that the cause is not a singular issue. High incidence of pertussis can therefore be seen as multi-factorial, including dramatic shifts in age distribution during large epidemics, improved detection as well as increased awareness in the reporting and better diagnosis of the disease. Hence, the control measures for pertussis have to be modified or vaccination schedules changed to reflect the current reality. As pertussis remains of international importance, it is posited here that efforts should be geared towards assessing long-term immunogenicity of the booster vaccine.

**Keywords:** Bordetella pertussis, outbreak, USA, control measures.

## Introduction

Pertussis, commonly known as whooping cough, is caused by the bacterium Bordetella Pertussis (Faulkner et al., 2011), which was first isolated at the beginning of the 20th century (Brooks and Clover, 2005). Bordetella Pertussis (B. Pertussis) is an exclusively human pathogen which can affect people of all ages. Transmission of the organism occurs as a result of close direct contact with an infected person (Dodhia et al., 2002). It is a highly contagious disease of the respiratory tract, with up to 90% of household contacts developing the disease (Hodder et al., 1992; WHO, 2013).

Pertussis is an endemic disease with an estimated 16 million cases world-wide: there were around 195,000 pertussis-related deaths in 2008 alone, with 95% of cases occurring in developing countries (Halpering 2001; WHO, 2010). Recently however, there have also been outbreaks of pertussis in some developed countries. In England and Wales there were 1,614 laboratory-confirmed cases of whooping cough in October 2012, bringing the total number of cases in the regions to 7,728 (HPA, 2012a). Pertussis, although a vaccine-preventable infection, is still an endemic disease in the US (Wendelboe et al., 2005; Hewlett et al., 2005; and Klein et al., 2012) but the prevalence of the disease had reportedly been under control since the 2005 outbreak (Rohani and Drake, 2011).

The Centre for Disease Control and Prevention (CDC) reported that the overall incidence of pertussis peaked at 27,550 cases in 2010 but stabilised at 18,719 cases in 2011 (CDC, 2012). However, increased cases of pertussis were reported in the majority of states, with 49 states reporting an increase in whooping cough in 2012 compared to 2011 (CDC, 2013a). The United States is currently experiencing what may turn out to be the largest outbreak of reported pertussis in recent times (CDC, 2012). Provisional counts from the pertussis surveillance system put the number at more than 41,000 including 18 pertussis-related deaths (CDC, 2013a). The outbreaks were recorded despite rates of immunization at more than 80% among the population (Hewlett et al., 2005). Receipt of five doses of diphtheria, tetanus and acellular pertussis (DTaP) is mandatory for children in the US (Klein et al., 2012). As demonstrated, the US continues to record increases in incidence of pertussis despite it being a vaccine preventable disease (HPA, 2013; CDC, 2013b). This essay will argue that pertussis outbreak in the US is due to declining immunity and therefore vaccination schedules need to be redefined. The epidemiological triangle will be used to demonstrate the implications of this decline.

## Discussion

While adolescents and adults tend to display mild symptoms of pertussis, young unimmunised infants especially under six months of age are the most vulnerable group with the highest rates of complication and death occurring in this age bracket (Altamirano et al., 2012; Health Protection Agency 2012). Also, while pertussis vaccines are highly recommended to children under seven years of age (Ward et al., 2005), the disease is also frequent among adults. Because pertussis



 
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continues to circulate among older persons, this creates a source of contagion through respiratory secretion for young children, with parents identified as the most common source of transmission (Birsgard et al., 2004; de Greeff et al., 2010; Jardine et al., 2010; CDC, 2013b). As will be discussed further, evidence suggests that the transmission of pertussis may result from declining immunity (Forsyth et al., 2004). This may be due to modest decrease in vaccine effectiveness although the results on long-term vaccine protection are not fully available yet (CDC, 2013c).

In 2010, California experienced its highest incidence of pertussis in more than 60 years (Klein et al., 2012; Misegades et al., 2012). The disease was found to be highly prevalent in the 8 to 11 year old age group despite high vaccination coverage (Klein et al., 2012). A study of association between childhood pertussis and vaccination (receipt of all five dose of DTaP) conducted by Misegades et al. (2012) concluded that, as the time elapsed since the last DTaP dose increased, so did the chances of contracting pertussis. This therefore demonstrates that routine childhood immunisations are successful in reducing incidence levels of pertussis.

Another study was conducted by Klein et al. (2012), the aim of which was to assess and quantify the waning of DTaP protection against pertussis over time in a highly vaccinated child population, who received DTaP rather than a whole-cell pertussis vaccine between the ages of 3 and 7 years. The waning immunity after DTaP was assessed using two analyses. The primary analysis compared Polymerase Chain Reaction (PCR) -positive case patients with PCR-negative controls; while the secondary analysis compared PCR-positive case patients with a matched control. The first and secondary analyses revealed similar result: there was a 42% increase each year in the odds of acquiring pertussis after the fifth dose of DTaP (Klein et al., 2012). This suggests that immunity against pertussis wanes as the time interval after the DTaP increases. A very recent study assessing the risk of pertussis by time since vaccination in the two states of Minnesota and Oregon was conducted by Tartof et al. (2013). The study identified an increase in incidence rates and risk ratios of reported pertussis in the six years after receipt of the fifth DTaP dose. This also strongly suggests waning of immunity against pertussis in the US (Tartof et al., 2013).

A similar study was carried out in Norway, a country with relatively high immunisation levels. The study showed that immunity against pertussis has declined with time, a decline more evident in recent years despite a considerable variance of waning immunity among the studied population (Lavine et al., 2012). Previous outbreaks of pertussis necessitated change within many countries -



 
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including Canada, the US and Norway- from the use of the whole-cell pertussis vaccine to a multi-component acellular pertussis (DTaP) (Vickers et al., 2006).

Although DTaP has proven to be effective in the prevention of confirmed cases of pertussis infections and is associated with fewer adverse effects than whole-cell pertussis (Romina and Edwards, 2012), this effectiveness has not been profound given the recent pertussis outbreaks in the US (Klein, 2012), Norway (Lavine et al., 2012) and UK (HPA, 2012a). This is despite the high nation-wide coverage of the multi-component acellular pertussis vaccine in these countries.

The three mentioned studies (Misegades et al., 2012; Klein et al., 2012; Tartof et al., 2013) thereby assert that declining immunity after the fifth dose of DTaP among children played a key a role in fuelling the recent pertussis outbreak in the US. Also, there is consistency in the position of the three studies which demonstrate that there is a progressive decrease in estimated vaccine effectiveness each year after the final dose of vaccination of pertussis vaccination. Vaccine effectiveness may not, then, be the only factor fuelling outbreak of pertussis.

Since the eradication of vaccine-preventable communicable diseases such as pertussis remains an important international public health goal, various studies have asserted that waning immunity is a contributory factor to the rising incidence of pertussis globally. It is therefore pertinent to assess the implications of this factor on public health. One such study was carried out in the Netherlands in the year 2000 which, using a mathematical model, investigated the role of sub-clinical infection and waning immunity in the transmission force of B. Pertussis (van Boven et al., 2000). Analysis of the model reveals that waning immunity tends to increase the prevalence of susceptibility in the population, and thus tends to decrease the dynamics of infection.

On the other hand, the study also states that if most infections are sub-clinical, the true incidence of pertussis will be higher than the observed incidence, hence increasing the force of infection (van Boven et al., 2000). The results of this study are contingent on two factors: the rate at which immunity is lost, and the percentage of infections that are sub-clinical (van Boven et al. 2000). Since vaccination remains a major preventive measure against pertussis, this also has implication(s) for public health. Based on empirical data from 64 countries across the five continents, frequent outbreaks of pertussis are associated with vaccine coverage (Broutin et al., 2010). A mathematical model of the analysis posits that if there is herd immunity, inter-epidemic periods of pertussis are



 
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expected to increase (Broutin et al., 2010). Does this then imply that pertussis is no longer vaccine-preventable?

While it could be argued that declining immunity is a contributory factor to the increase in the incidence of pertussis, the recent increase cannot be attributed to declining immunity alone. As the study by Klein et al. (2012) reveals, there is a sharp increase in the incidence of pertussis among children 8 to 11 years in California, followed by a sharp decrease among children aged 12 to 15 years. The study further states that the result is not characteristic of the epidemiology of pertussis in previous outbreaks (Klein et al., 2012). This may confirm the assertion of Cherry et al. (2012) that the infection rate burden of pertussis is unknown. This could partly be due to other pathogens which cause symptoms similar to pertussis (Faulkner et al., 2011; CDC, 2013a); hence, determining who has pertussis and who does not is difficult to ascertain. Due to different diagnoses across different areas, there is also no standardised laboratory diagnosis for B. Pertussis (Kretsinger et al., 2006; von Konig et al., 2002) and cultural studies which are the main standard have been superseded by the speed of PCR (Mandal et al., 2012). The study, while investigating the laboratory contamination responsible for pseudo-outbreak in the US in 2009, suggests that lack of PCR cut-offs for detecting weakly contaminant DNA is a contributory factor for the outbreak (Mandal et al., 2012).

However, a recent clinical case definition has been designed to increase sensitivity for detecting pertussis cases when a confirmatory laboratory test is negative (Faulkner et al., 2011). The increase in the incidence of pertussis therefore could also be due to improved detection as well as increased awareness in the reporting and better diagnosis of the disease (Forsyth et al., 2004; Faulkner et al., 2011). A similar study based on the data collected in England and Wales posits that loss of natural immunity may not be the primary driver of the rising incidence of pertussis (Wearing and Rohani, 2009). The study suggests that attention should instead be focussed on pathogen evolution and perturbations in vaccine manufacture, uptake and efficiency (Wearing and Rohani 2009).

Similarly, a recent study in Sweden suggested that waning immunity appears to be a less important factor for high incidence of pertussis. The study asserts that age-specific contact patterns, with high levels within certain age-groups and between parents and children, are all that is necessary to explain the epidemiology of prevalence of pertussis (Rohani et al., 2010).



 
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Another recent study in the US revealed that the rising incidence of pertussis can be explained beyond age-specific contact patterns and declined immunity (Schmidtke et al., 2012). The study divided 661 B. Pertussis isolates collected in the US between 1935 and 2009 into eight periods relating to introduction of novel vaccines or change in vaccination schedule. It found a degree of variation in B. Pertussis population in period three -1970s and 1980s- and also further suggested that, given the fact that it has no non-human hosts or environmental niches, vaccine-mediated immunity is the most likely factor for the selective pressure against B. Pertussis. The study concludes that vaccine-induced virulence evolution may be a factor responsible for the variation in B. Pertussis population (Schmidtke et al., 2012). This conclusion is similar to the evidence found in World Health Organisation's (WHO) position paper, stating that B. Pertussis may alter their phenotypic state, thereby showing different expressions of virulence factors (WHO, 2010). This virulence evolution may therefore be responsible for the high incidence in pertussis.

As evidenced above, the high incidence of pertussis in the US goes beyond the issue of declining immunity and is therefore multi-factorial, including dramatic shifts in age distribution during large epidemics (Klein et al., 2012). In line with this, the control measures for pertussis have to be modified or vaccination schedules changed to reflect the current reality. The existing control measures in the US recommend that the first three shots of DTaP are given to infants at 2, 4 and 6 months of age. The fourth and fifth shots are given at 15 through 18 months and 4 through 6 years respectively (CDC, 2013b). Preteens in the US, who missed the earlier vaccinations and adults, are to be given a single dose of Tdap booster vaccine (Kretsinger et al., 2006).

Several positions have been put forward for mass vaccination of the population (Forsyth et al., 2004; Lavine et al., 2012). With parents and close family members serving as sources of contagion to young infants, vaccination of adults with Tdap has been recommended, especially for those who have close contact with infants (de Greeff et al., 2010; Jardine et al., 2010). Tdap as a booster immunization was licensed in the US for persons aged 11 – 64 years (Kretsinger et al., 2006). It has been proven to be effective and safe, particularly if the recipients have received tetanus diphtheria or tetanus toxoid immunization (Td/TT) more than 2 years earlier (Kretsinger et al., 2006, Talbot et al. 2010). As part of the control measure and in addition to adult booster immunization (Tdap), the Advisory Committee on Immunization Practice (ACIP) of the CDC also recommended cocooning of infants (Kretsinger et al., 2006).



 
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Cocooning is the targeted immunization of post-partum women and all contacts of their infants during the first year of life, before their birth or during hospital discharge (Healy and Baker 2012). The ACIP recommendation is based on similar proposal from other countries and is in line with the recommendation from Global Pertussis Initiative (GPI) (Forsyth et al., 2007). However, as Healy and Baker (2012) posit, cocooning is cost-effective but it has some fundamental constraints. It is limited in its ability to prevent infant pertussis in the first few weeks of life because the disease may be circulating in a household at the time of birth.

Secondly, cocooning is a logistically difficult measure to implement (Healy and Baker, 2012), a position supported by a similar study conducted in Canada by Skowronski et al. (2012). The study revealed that pertussis related morbidity is uncommon; hence the clinical course typically includes full recovery without residual disability. Therefore, the number needed to vaccinate (NNV) estimates that parental pertussis cocoon immunization can be used to produce some estimate costs.

Multiplying the NNV by immunization costs (vaccine + administration > $20 [Canadian Dollars]) shows that the cost per infant hospitalization (~$200,000), intensive care unit (ICU) admission (>$2 million), or death (>$20 million) prevented through parental pertussis immunization seems to be significantly high (Skowronske et al., 2012). However, evidence shows that even if mass pertussis vaccination including cocooning is embarked upon, some constraints still exist. The fact that pertussis susceptibility increases as the interval from the last scheduled vaccination increases, will lead to a reduced level of herd immunity, resulting in greater risk of acquisition (Witt et al., 2012).

According to Romina and Edwards (2012), it is not entirely clear what the implication of widespread uptake of the booster doses (Tdap) in the recommended age groups in the US will be, but data from Australia asserts that Tdap could have an impact on the total disease burden. A study by Witt et al. (2012) further suggests that the current pertussis vaccine doses seem not to be sufficient enough to prevent outbreaks of pertussis. This is similar to the conclusion reached by Romina and Edwards (2012) that it is not evident that a single booster dose of Tdap in adolescents and adults can confer lifelong immunity. The question now is, how best can we protect the populace from high incidence of pertussis?

Witt et al. (2012) and Romina and Edwards (2012) state that consideration should be given to the possibility of earlier or numerous doses -initial vaccination and booster vaccination- of acellular



 
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vaccine for both infants and adults as part of the routine immunization scheduled. Additionally, since evidence portends that pertussis is most severe among young infants (Altamirano et al., 2012; HPA, 2012b), the current vaccination schedule, which administers the first dose of pertussis vaccine no earlier than six weeks, leaves some windows of susceptibility. This reinforces the conclusion of Romina and Edwards (2012) that the possibility of clinical administration of pertussis vaccination to infants younger than six weeks should be explored.

## Conclusion

Pertussis, despite being a vaccine-preventable disease, continues to exert a considerable burden on public health, with significant morbidity in highly vaccinated populations. While evidence that declining immunity is responsible for increased incidence of pertussis in the US is not conclusive, there is a strong indication that declining immunity plays some role in influencing the rising incidence of the disease. To this extent, vaccination remains an effective global measure against pertussis. In the meantime, efforts should be geared towards assessing long-term immunogenicity of the booster vaccine. This will help in determining whether there is a need for repeated doses or not. If the immunogenicity is found to be relatively short, a pertussis containing vaccine providing long-lasting immunity should be advocated. However, because the development of a new vaccine remains in the distant future, the need to intensify on-going assessments of the determinants of declining immunity with acellular vaccine is of immediate importance.

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